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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,140	BRINES ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-10,12-16,24-46 and 53-55* is/are pending in the application.

4a) Of the above claim(s) *1-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10,12-16,24-46 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/27/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's response and amendments filed 6/27/2008 is acknowledged and entered. Claims 1-5, 8-10, 12-16, 24-46, and 53-55 are pending. Claims 6-7, 11, 17-23, and 47-52 have been cancelled by Applicant. New claim 55 has been added. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 8-10, 12-16, 24-46, and 53-55 are under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 6/27/2008 has been considered. A signed copy of the IDS is attached hereto. It is noted that many of the references submitted in the 6/27/2008 IDS are duplicates of references that have already been submitted.

Response to Arguments

Claim Objections/Rejections Withdrawn

3. Rejections drawn to claims 11 and 17-23 are withdrawn as moot in light of the cancellation of these claims.

4. The rejection of claims 8-46 and 53-54 under 35 U.S.C. 112, first paragraph, because of the phrase "a generic tissue protective cytokine," (i.e. Part I) is withdrawn in light of Applicant's amendments. However, the rejection under 35 USC 112, first paragraph over claims 8-10, 13-16, 43-46, and 54-55 (i.e. part II and as applicable to new claim 55), because of structural insufficiency is maintained, as set forth below.

5. The rejection of claims 8-10, 13-16, 43-46, and 54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn as moot in light of Applicant's amendments. However, a new written description rejection over amended claim 8 is set forth below.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-10, 13-16, 43-46, and 54-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling in the art for a method of treating inflammatory disease in a mammal comprising administering a chemically modified erythropoietin or recombinant Epoetin Alpha with a glucocorticoid, dexamethasone, or a cytokine such as IFN-β, does not reasonably provide enablement for the claimed method comprising a broad genus of structurally generic modified EPO variants having a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin, and it does not reasonably provide enablement for generic "immunomodulatory" agents, for the reasons of record and the reasons set forth herein.

Applicant argues that the two declarations of Dr. Michael Brines dated 5 December 2007 and 20 February 2008 show that no undue experimentation would be required to practice the claimed methods (Remarks, page 12, second paragraph). Applicant argues that no undue experimentation would be required to generate the chemically modified forms of EPO recited in claims 35 and 37 (Remarks, page 13, first paragraph). Applicant argues that paragraph 91 of the specification (page 29) teaches four regions in the EPO protein (SEQ ID NOs: 1-4) that can be modified to reduce EPO's erythropoietic activity (Remarks, page 13, fourth paragraph). Applicant argues that these teachings disclose that basic amino acid residues arginine and lysine can be modified to achieve reduced erythropoietic activity (Remarks, page 13, fourth paragraph). Applicant cites Satake, 1990, for the proposition that modification of lysine residues to neutral or negative charges results in non-erythropoietic EPO (Remarks, page 13, last paragraph). Applicant argues that a wide range of chemical modifications to EPO permit EPO to retain its tissue-protective activity, as determined by the middle cerebral artery occlusion test (Remarks, page 14, first through third paragraphs). Applicant argues that carbamylation of EPO, a form of lysine modification, also permits the modified EPO to retain tissue-protective activity (Remarks, page 14, fourth paragraph). Applicant argues that the Cuzzoncrea and Savino references demonstrate that chemically modified forms of EPO are tissue-protective and retain their anti-inflammatory effect (Remarks, page 15, last paragraph to page 16). Applicant argues that the Diem reference (particularly Figure 1 F) demonstrates synergism of EPO and methyprednisolone (MPred) restores visually evoked potentials in the visual cortex, but that neither drug alone restores visually evoked potentials (Remarks, page 16, third and fourth paragraph). Applicant argues that Gorio is consistent with the workability of the claimed methods (Remarks, p. 16, last paragraph to first paragraph of page 17). Applicant's arguments have been

fully considered and they are persuasive in part, as to specifically claimed EPO modifications (i.e. claims 35 and 37, for example), but they are not persuasive over several of the other claims, including independent claim 8.

Although several of the examiner's previous concerns have been addressed by the instant claim amendments, Applicant has still not provided sufficient guidance to teach one of ordinary skill in the art how to make or use the invention commensurate in scope with the claims. For example, claim 8 has been amended in part to incorporate the subject matter of now-cancelled claim 11. The incorporation of the subject matter of claim 11 into independent claim 8 has not provided any additional substantive clarity as to the structural requirements of the genus of modified erythropoietins having the requisite biological activities. The instant disclosure does not provide sufficiently definitive structure for the broad genus modified EPO variants set forth in claim 8, such that a person of ordinary skill in the art could make or use the modified variants. Claim 8, subparts (i)-(v) state that modifications may be made to one or more arginine residues, lysine residues, tyrosine residues, aspartic acid residues, glutamic acid residues, tryptophan residues, or made to the N-terminal amino group. These modifications are not limited to chemical modifications, but also include amino acid substitutions, deletions, and additions. Applicant previously argued that examples of methods for chemically modifying EPO such as "guanidation, amidination, carbamylation(carbamoylation), trinitrophenylation, acetylation, succinylation, nitration, among others are provided at p. 29, lines 11-21" and that examples of these modifications and others are set forth at "e.g. p. 32, line 21 to p. 38, line 9. (Remarks, p. 17, third paragraph). Although these examples are set forth in the specification, and the claims are read in light of the specification, the examiner may not incorporate limitations from the specification into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Compare claims 12, 24-42 and 53, which recite specific structural modifications which are well known and taught in the art (see i.e. Satake et al., and Brines et al., (2000), previously cited of record). It is noted that Applicant does not present arguments about generic modifications of one or more tyrosine, aspartic acid, glutamic acid, or tryptophan amino acid residues, as presently recited in amended claim 8, subparts (iii)-(v).

The examiner acknowledges that the specification recites general information on the generic modifications of EPO, including amino acid sites to modify by “at least one modification” (specification p. 14, paragraph 31). The examiner also agrees that a general knowledge of protein modification is also known in the art. However, modifications of amino acid residues may include addition, deletion, substitution, or truncation modifications. The generic recitation in the specification at page 14, paragraph 31, and the generic claim language (see especially claim 8) of “one or more modified [insert recited

residue]…" is not sufficient guidance to give a person of skill in the art so that they would know how the sites could be modified and the manner of the modification, such that the modified protein would have the claimed biological function. It is also important to clearly establish that the art of record (see Office Actions of 28 March 2007 and 27 December 2007) specifically states that even single amino acid modifications of proteins, especially cytokines, directly affects protein function. In the instant case, Applicant has simply not provided sufficient guidance to enable a person of skill in the art to make and use the genus of generic modified EPO variants with "one or more" modifications to the recited amino acid residues. The functional results of an unknown generic "modification" of these residues are not reasonably predictable. One of skill in the art would only be able to test the function of structurally known variants using routine experimentation once the structure was known. A generic recitation of modifying "one or more" residues does not provide enough guidance to make a structure-function assessment predictable.

The biological function of the broad genus of EPO variants cannot be predictably ascertained from the limited disclosure in the specification or from what is known in the art because the art teaches that the structure of the EPO variants is critical to whether the modified protein is biologically functional in terms of whether it binds to the EPOR-beta heterodimer, the EPOR homodimer, or both, or whether it binds to the EPOR-beta heterodimer with a reduced level *in vivo*, compared to native erythropoietin. Because of the requirements for the specific structure-function correlation, it would require undue experimentation for a person of skill in the art to make the large genus of claimed EPO variants and test the same for activity. For example, although the native sequence of EPO is known, one of skill in the art would not understand how to generically "modify" the N-terminal amino group as recited in claim 8, subpart (ii). There is no teaching of what to do in order to achieve this generic modification. It is understood that N-terminal chemical modifications are taught in the art and in the specification, but the claims, as written, encompass more than chemical modifications. One skilled in the art cannot readily anticipate the *in vivo* biological effect of the claimed invention on a mammalian subject in light of the generic structures taught in claim 8

Of particular interest to the examiner is Dr. Brines' declaratory statement in numbered paragraph 24 in the 20 February 2008 declaration at page 8, which states that "chemically modified, non-erythropoietic, tissue protective forms of EPO can exert tissue-protective activity in any erythropoietin-responsive tissue, i.e. any tissues that expresses an [sic] Tissue-Protective Receptor Complex." (page 8 of both declarations) [Emphasis added]. This was the understanding of the examiner during the video teleconference interview with Applicants and their representatives held on 21 May 2008. It is understood

by the examiner that it is the intent of the inventors that the claimed genus of EPO structural derivatives bind to the EPOR-beta receptor heterodimer and bind the EPOR homodimer at a reduced level such that they have a reduced or absent erythropoietic activity. Insofar as the claims of a patent application are supposed to confer this intent, instantly amended claim 8 falls short. Applicant is requiring that the genus of modified EPO variants have a specific function, that function being that they have a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin, which is testable by the recited assays. However, instant claim 8 recites only generalized, generic modifications such that a person of ordinary skill in the art would be required to make a sufficient representative number of variants with the recited modifications and test the same for activity. Modifications of the recited amino acid residues, as claimed, may include addition, deletion, substitution, or truncation modifications and are not limited to the chemical modifications discussed in Dr. Brines' declaration.

Because the claimed function of the genus of variants is specific (showing reduced level of *in vivo* erythropoietic activity compared to native EPO), determining whether any particular generic modification to any one or more residues would be unpredictable. The lack of structural distinctness in the claimed genus of variants in claim 8 is an invitation to experiment in an unpredictable area of molecular biology, where the art teaches that minor modifications of protein structure cause critical problems with protein functionality (see art cited of record).

The biological function of the broad genus of EPO variants cannot be predictably ascertained from the limited disclosure in the specification or from what is known in the art because the art teaches that the structure of the EPO variants is critical to whether the modified protein is biologically functional in terms of whether it binds to the EPOR-beta heterodimer, the EPOR homodimer, or both, or to the EPOR-beta heterodimer with a reduced level *in vivo*, compared to native erythropoietin. Because of the requirements for the specific structure-function correlation, it would require undue experimentation for a person of skill in the art to make the large genus of claimed EPO variants and test the same for activity. For example, although the native sequence of EPO is known, one of skill in the art would not how to generically "modify" the recited residues by deletion, addition, substitution, or truncation in order to achieve the claimed biological effect.

Regarding the examiner's concern over claim 8, subpart (b), Applicant's Example 12 shows the administration of commercially available recombinant EPO (PROCRIT) co-administered with dexamethasone in EAE rats. Example 12 notes that the EPO delayed the onset of disease in a dose dependent fashion, but did not delay the time to greatest severity (paragraph 319, p. 113). Paragraph 320 of Example 12 also states that no relapse was seen after withdrawal of EPO, such as those seen after

withdrawal of dexamethasone. However, it is unclear from paragraph 320 whether there was any relapse after withdrawal of concomitantly administered EPO and dexamethasone. Paragraph 320 suggests that the withdrawal symptoms were observed when one or the other drug was used individually, but it is silent as to whether there was any relapse when the drugs were used together (compare new claim 55).

Applicant argues that the Cuzzoncrea and Savino references demonstrate that chemically modified forms of EPO are tissue-protective and retain their anti-inflammatory effect (Remarks, page 15, last paragraph to page 16). With regard to the Cuzzoncrea et al., reference, the examiner maintains that it is non-analogous art with respect to the full scope of the claims as written. Cuzzoncrea et al., discuss the co-administration of EPO with CII (collagen type II), which is a proteinaceous agent (compare claim 10). The administration of the type II collagen induced rheumatoid arthritis in mice, rather than treating a disease. The Cuzzoncrea reference meets the limitations of instant claims 8 and 10, but the teachings of the reference appear to be in conflict with the intent of the inventors. The scope of the claims, as written, encompass "immunomodulatory" agents that cause or exacerbate inflammatory disease, which is contradictory to the preamble of the claims. Additionally, Cuzzoncrea et al., do not discuss reduced or non-erythropoietic EPO variants in combination with immunomodulatory agents, but instead discuss only administration of recombinant human EPO. With regard to Savino et al., it is also non-analogous art. Savino et al., investigated carbamylated EPO and asialylated EPO, but not in conjunction with an anti-inflammatory or immunomodulatory drug (compare instant claim 8, subpart (b)).

Applicant argues that the Diem et al., reference (particularly Figure 1F) demonstrates synergism of EPO and methyprednisolone (MPred) restores visually evoked potentials in the visual cortex, but that neither drug alone restores visually evoked potentials (Remarks, page 16, third and fourth paragraph). With regard to the Diem et al., reference, the authors state that one of the aims of their study was to test the hypothesis that MPred and EPO would have synergistic effects when co-administered (p. 376, last paragraph of the introduction). However, if one reads farther into the paper, one will see that the authors state that "late, short-duration EPO was beneficial when treatment was combined with high-dose MPred therapy....although beneficial effects of MPred on axon counts can also be seen if MPred was given as monotherapy" (p. 383, column 2, last paragraph to p. 384, first paragraph, and lines 4-6 of paragraph 2, column 1). Diem et al., suspect that the suppressing effect of EPO on the production of proinflammatory cytokines during early development of EAE synergistically enhances MPred-induced tissue protection, but there is insufficient data in their paper to support this assertion (p. 384, column 1, last sentence of second paragraph). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism").

Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a "greater than additive effect" is not necessarily sufficient to establish synergy because such an effect can either be expected or unexpected. In the case of Diem et al., it is unclear whether the effect of the combination of EPO and MPred was merely the actions of each of the drugs additively, but not synergistically. In support of this argument, Diem et al., also note that the administration of EPO as an exogenous neurotrophin-like substance may compensate for the lack of endogenous neurotrophic factor support resulting from anti-inflammatory treatment of EAE or multiple sclerosis (p. 384, column 2, end of first paragraph). The unknown variables and lack of sufficient data in Diem et al., do not permit the use of the reference as evidence of a synergistic effect.

Regarding Applicant's argument that Gorio is consistent with the workability of the claimed methods (Remarks, p. 16, last paragraph to first paragraph of page 17). Gorio et al., (previously cited of record) teaches that methylprednisolone sodium succinate (MPSS) neutralizes the beneficial effects of erythropoietin in experimental spinal cord injury. Using a rat model of contusive SCI, the authors compared the effects of EPO [500-5,000 units/kg of body weight (kg-bw)] with MPSS (30 mg/kg-bw) for proinflammatory cytokine production, histological damage, and motor function at 1 month after a compression injury. Although high-dose EPO and MPSS suppressed proinflammatory cytokines within the injured spinal cord, only EPO was associated with reduced microglial infiltration, attenuated scar formation, and sustained neurological improvement. "Unexpectedly, coadministration of MPSS antagonized the protective effects of EPO, even though the EPO receptor was up-regulated normally after injury" [Emphasis added]. Gioro et al., specifically disclaims the coadministration of glucocorticoids, saying that concurrent administration should be avoided Gioro et al., provides evidence of the lack of predictability of co-administering EPO or a variant thereof with a generic immunomodulatory or anti-inflammatory agent, such as a glucocorticoid.. Insofar as the teachings of Gorio et al., provide evidence of inoperative embodiments of the instantly claimed invention (as written), Applicant is reminded that broad claims may be rejected merely because they read on a significant number of inoperative species when examiner sets forth reasonable grounds in support of his or her conclusions that the claims may read upon inoperative subject matter. At that point, it is incumbent upon applicant either to reasonably limit claims to approximate area where cooperativeness has not been challenged or to rebut examiner's challenge by submission of representative evidence or by persuasive arguments based on known laws of physics and chemistry (In re Cook and Marigold, 169 USPQ 298 (CCPA 1971)). The breadth of Applicant's claims, as written, render the claims unpredictable because it would require undue experimentation for one of skill in the art to make and/or use the invention as claimed.

Additionally, the examiner is concerned about the amendment to claim 8 reciting that the genus of modified variants have a "reduced level" of *in vivo* activity, when claim 54 recites that the erythropoietin is "non-erythropoietic." The examiner's concern arises because Applicant uses the phrase "reduced *in vivo* erythropoietic activity" as having equivalent meaning with "non-erythropoietic forms of EPO" in the Remarks filed 6/27/2008, page 12, and footnote 1. Applicant's Footnote 1 remarks render the terms "reduced level" and "non-erythropoietic" interchangeable and therefore without distinct meaning. Clarification is requested.

Due to the large quantity of experimentation necessary to generate the claimed genus of modified EPO variants and screen same for activity for use in the claimed method, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the lack of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

New Claim Rejections

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

8. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19 USPQ2d 1111, (Fed. Cir. 1991), states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a broad genus of generic, structurally modified EPO variants having a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There are several species of chemically modified EPO that are disclosed in the art and the specification that are within the scope of the claimed genus. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

The instant disclosure does not provide sufficient description of the structural requirements for the broad genus modified EPO variants set forth in claim 8. Claim 8, subparts (i)-(v) state that modifications may be made to one or more arginine residues, lysine residues, tyrosine residues, aspartic acid residues, glutamic acid residues, tryptophan residues, or made to the N-terminal amino group. Although it is noted that examples of methods for chemically modifying EPO, such as guanidation, amidination, carbamylation(carbamoylation), trinitrophenylation, acetylation, succinylation, and nitration, among others are provided at p. 29, lines 11-21; p. 32, line 21 to p. 38, line 9, the claims are read in light of the specification, the examiner may not incorporate limitations from the specification into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Compare claims 12, 24-42 and 53, which recite specific structural modifications and are specifically disclosed. While "examples explicitly covering the full scope of the claim language" typically will not be required, a sufficient

number of representative species must be included to "demonstrate that the patentee possessed the full scope of the [claimed] invention." Lizardtech v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

The examiner acknowledges that the specification discloses general information on the generic modifications of EPO, including amino acid sites to modify by "at least one modification" (specification p. 14, paragraph 31). The examiner also agrees that a general knowledge of protein modification is also known in the art. However, modifications of amino acid residues may include addition, deletion, substitution, or truncation modification. The generic disclosure in the specification at page 14, paragraph 31, and the generic claim language of claim 8 of "one or more modified [insert recited residue]…" is not sufficient to adequately describe the structure of the modified EPO to a person of skill in the art so that they would be aware that Applicant was in possession of the full scope of the genus of generically modified arginine, lysine, tyrosine, aspartic acid, glutamic acid, and tryptophan amino acid residues or N-terminal amino group modifications. Applicant has not provided an adequate biologically functional structural description of these generic EPO variants to demonstrate to a person of skill in the art that Applicant was in possession of a sufficient representative number of modified EPO variants that have the requisite function of having reduced or non-erythropoietic *in vivo* activity compared to native EPO.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a broad genus of generic, structurally modified EPO variants having a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kuban, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1). The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear whether claim 13 provides an additional limitation to claim 8. Claim 13 recites the method of claim 8 wherein erythropoietin "is capable of" traversing an endothelial cell barrier. The "capable of" language renders the claims indefinite because it is unclear whether this is an inherent property of the genus of claimed modified EPO variants.

11. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 9 recites the broad recitation of the genus of steroids in line 2, and the claim also recites subgenera/species of glucocorticoids and corticosteroids which is the narrower statement of the range/limitation.

12. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 has been amended to recite that the genus of modified variants have a "reduced level" of *in vivo* activity, when claim 54 recites that the erythropoietin is "non-erythropoietic" and Applicant uses the phrase "reduced *in vivo* erythropoietic activity" in reference to "non-erythropoietic forms of EPO" in the Remarks (Remarks, page 12, footnote 1). Applicant's Footnote 1 remarks render the terms "reduced level" and "non-erythropoietic" interchangeable and therefore without meaning. Clarification is required.

Obviousness-Type Double Patenting Rejections

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 8-10, 12-16, 25, 43, 54, and 55 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,531,121 (11 March 2003, benefit to 29 December 2000). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same or overlapping subject matter. Claims 1-15 of the '121 patent are drawn to methods for enhancing disorders caused by ischemic processes. Instant claims 8 and 43 establish that the inflammatory disease results from a disease condition or trauma. Instant claims 15 and 16 correlate with the cell types recited in the claims of the '121 patent. The claims of the '121 patent are drawn to administering asialoerythropoetin (compare instant claim 12). The '121 patent also teaches methods of *in vivo* treatment using non-erythropoietic forms of erythropoietin (column 2, lines 15-39 and column 3, lines 44-46) (compare instant claim 54). Administration of the anti-inflammatory or immunomodulatory agent, dexamethasone (a small molecule) (compare instant claims 8-10) with EPO is taught at column 16, lines 58 and 63-67 (compare instant claims 8 and 55). The '121 patent also teaches that EPO crosses the blood-brain barrier in Example I (column 18). Phenylglyoxal-erythropoietin is taught in Example 5 (column 20-21) (compare instant claims 12 and 25). Applicant is reminded that MPEP § 804 (II) states, "When considering whether the

invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure." (Emphasis added). "Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970)."

15. Claims 8, 13-16, 31, 32, and 43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 37, 38, 50-60 of copending Application No. 10/188,905. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same or overlapping subject matter. Both sets of claims are drawn to a method of treatment comprising administering a modified EPO. Both methods recite the transitional phrase "comprising" and as such, the methods may comprise additional steps which are not specifically recited by either application. Claims 38 and 56 of the '905 application are drawn to trauma and inflammatory diseases (compare instant claims 8 and 43). Claims 50 and 51 of the '905 application are drawn to the same subject matter as instant claims 13 and 14. Claim 53 of the '905 application is drawn to the same subject matter as instant claims 15 and 16. Claims 54-55 and 57-60 of the '905 application are drawn to the same subject matter as instant claims 31 and 32.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 8, 15, 16, 28-31, 33, 34, 36, 39, 53, and 54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 14, 16-21, 25, 28, 29, 61, 62, and 63 of copending Application No. 10/185,841 in view of Brines et al., (PNAS USA, 2000 Sept 12; 97(19):10526-10531) (previously cited of record). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same or overlapping subject matter. Both sets of claims are drawn to a method of treatment comprising administering a modified EPO. Both methods recite the transitional phrase "comprising" and as such, the methods may comprise additional steps which are not specifically recited by either application. Claim 1 of the '841 application teaches the same subject matter as instant claim 8. Claim 14 of the '841 application

teaches the same subject matter as instant claims 28 and 29. Claim 16 of the '841 application teaches the same subject matter as instant claim 30. Claim 17 of the '841 application teaches the same subject matter as instant claim 31. Claim 18 of the '841 application teaches the same subject matter as instant claim 33. Claim 19 of the '841 application teaches the same subject matter as instant claim 34. Claim 20 of the '841 application teaches the same subject matter as instant claim 36. Claim 21 of the '841 application teaches the same subject matter as instant claim 39. Claims 25 and 28 of the '841 application teaches the same subject matter as instant claims 15 and 16. Claim 29 of the '841 application teaches the same subject matter as instant claim 8. Claim 60 of the '841 application teaches the same subject matter as instant claims 8 and 53. Claim 61 of the '841 application teaches the same subject matter as instant claims 8 and 31. Claim 62 of the '841 application teaches the same subject matter as instant claim 31. Claim 63 of the '841 application teaches the same subject matter as instant claim 54. Brines et al., teach methods of treatment with a composition comprising recombinant Epoitin alpha in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids or IFNβ (p. 10526, column 2, second paragraph; p. 10527, column 2, third paragraph; p. 10529, column 2, second paragraph; p. 10530, column 1, second paragraph; and p. 10531, column 2, second paragraph). It would have been obvious to a person of ordinary skill in the art to administer glucocorticoids or IFNβ in addition to the chemically modified EPO because of the suggestions, motivations, and teachings of Brines et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 8-10, 12-16, 24-46, and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Escary, WO 02/085940 (31 October 2002, benefit to 21 December 2001), Satake et al. (Biochimica et Biophysica Acta. 1990;1038:125-129) (previously cited of record), and Brines et al., (PNAS USA, 2000 Sept 12; 97(19):10526-10531) (previously cited of record).

The Examiner finds the following facts:

a. The instant claims are drawn to a method for treating an inflammatory disease in a mammal comprising responsive cells comprising administering a modified EPO and one or more anti-inflammatory or immunomodulatory agents.

b. Escary teaches a method of treating an individual with inflammatory disorders comprising administering a composition comprising a D70N erythropoietin variant (having a modified aspartic acid residue at position 70 of the amino acid sequence, see Figures 1A and 1B) at claims 22 and 23 (see also pages 28-35, especially 34, lines 17-33) (compare instant claim 8). Administration with interleukins and interferons (immunomodulatory proteins) are taught at page 32, lines 17-19 (compare instant claims 8 and 10). Treatment of rheumatoid arthritis is taught at page 29, line 18 (compare instant claim 44).

c. Escary does not teach chemically modified erythropoietins.

d. Satake et al. teach multiple embodiments of biologically active erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule. Satake et al. teach that guanidination of amino groups of the lysine residues using 2,4,6,-trinitrobenzenesulfonic acid and its organic salt is taught at p. 125, column 2, last paragraph; abstract; and p. 127, paragraph 4 and 5 (compare instant claims 38 and 39). Guanidination, amidation, carbamylation, trinitrophenylation, acetlyation, succinylation,

modification of arginine residues with 2,3-butanedione, nitration, and modification of carboxyl groups are taught at p. 126, column 1; p. 128, Discussion; and Table 1 (compare instant claims 24-27, 31-37, 41, and 53). Modification with phenylglyoxal is taught at p. 126, column 1; and Table 1 (compare instant claims 12 and 25). Modification of lysine residues by various lysine specific reagents are taught at page 128, column 2, Discussion (compare instant claim 30). Modifications of tyrosine residues are taught at page 128, column 2, Discussion (compare instant claim 40). Modifications using glycinamide are taught at page 126, column 1, ninth paragraph) (compare instant claims 41 and 42).

e. Brines et al., teach methods of treating inflammation in Female Lewis rats due to blunt force trauma injury (compare instant claim 43) with a composition comprising recombinant Epoitin alpha in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids or IFNβ (p. 10526, column 2, second paragraph; p. 10527, column 2, third paragraph; p. 10529, column 2, second paragraph; p. 10530, column 1, second paragraph; and p. 10531, column 2, second paragraph) (compare instant claims 8-10). The cells of instant claim 16 are encompassed within the composition comprising the Female Lewis rats who received the administration of the composition of claim 8. Brines et al., also teach that biotinylated recombinant human EPO crosses the blood-brain barrier (p. 10528, columns 1 and 2) (compare instant claims 13, 14, 28 and 29). Responsive cells, including neuronal cells, are taught at p. 10528, columns 1 and 2 (compare instant claim 15). Inflammation resulting from glial cells are taught by the EAE models at p. 10527, column 2, third paragraph, and p. 10530, column 1, second paragraph (compare instant claim 45). Inflammation triggered by apoptosis is taught at p. 10531, column 1, last paragraph to column 2, first paragraph (compare instant claim 46).

f. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

In view of the facts recited above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention. Escary teaches a method of treating an individual with inflammatory disorders comprising administering a

composition comprising a D70N erythropoietin variant with interleukins and interferons (immunomodulatory proteins) to treat rheumatoid arthritis. Escary does not teach chemically modified erythropoietins. Although Escary does not specifically disclose that the D70N EPO variant has a reduced level of in vivo activity, compared to native EPO, this activity is amenable to testing. Because the Patent Office does not have the facilities to determine whether the D70N EPO variant has the requisite biological activity required in instant claim 8, the burden is on the application to show a novel and unobvious difference between the claimed scaffold and that of the prior art. See In re Brown, 59 CCPA 1036, 459 F.2d. 531, 173 USPQ 685 (CCPA 1972) (holding at 1041, "[a]s a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith") and Ex parte Gray, 10 USPQ 2d 1922, 1924-25 (PTO Bd. Pat. App. & Int.). Escary meets all of the other limitations of instant claims 8-10.

Satake et al. teach multiple embodiments of biologically active erythropoietin having modifications of the instantly claimed amino acids comprising guanidination, amidation, carbamylation, trinitrophenylation, acetlyation, succinylation, modifications. Brines et al., teach methods of treating inflammation in mammals due to blunt force trauma injury with a composition comprising recombinant Epoitin alpha in an isotonic sodium chloride/sodium citrate and administration of glucocorticoids or IFNβ Brines et al., also teach that biotinylated recombinant human EPO crosses the blood-brain barrier.

The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a D70N or chemically modified EPO variant for use in a method of treating inflammatory disease, as evidenced by the teachings of Escary, Satake, and Brines. One of skill in the art would have recognized that the results of administering a combination of a D70N EPO variant or chemically modified EPO variant taught by Satake in a method of treating an inflammatory disease, as taught by Escary, would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to simply substitute one known element for another to obtain predictable results. One of ordinary skill in the art could have reasonably substituted a chemically modified EPO taught by Satake with the D70N EPO variant taught by Escary in a method of treating inflammatory disease with a reasonable expectation of success. Both the level of skill in the art in the field of molecular biology and the actual use if aspartic acid EPO variants in the method of treatment (as taught by Escary and Brines) make the substitution predictable. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the

very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious)

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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